

### REMARKS/ARGUMENTS

The instant invention concerns novel methods for the synthesis of oligonucleotides. The instant invention overcomes deficiencies in the synthesis art by allowing high yield coupling of phosphoramidite synthons to an oligomer chain that contains at least one unprotected phosphoryl protecting group (see page 5, lines 12-22). In particular, the invention concerns a support bound oligomer having at least one unprotected phosphate, phosphorothioate, or phosphorodithioate internucleoside linkage and certain neutralizing agents.

Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, 103, and 104 are pending. Claim 48 is amended. No claims are added or canceled.

Claims 48-52, 56-60, 66, 81-85, 92-95, and 104 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. While not agreeing with the rejection, Applicants have amended claim 48 to recite certain 2'-substitutents in order to advance prosecution. The basis for this amendment can be found, for example, at page 29, line 13 to page 31, line 5. In regard to the objection to the inclusion of variables  $R_4$  and  $R_5$  in claim 48, these variables were canceled in the September 4, 2003 amendment. As such, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 1-6, 11-15, 21, 36-40, 47-52, 66, 81-85, 92-97, and 104 are rejected as allegedly obvious under 35 U.S.C. § 103(a) over Caruthers et al., Proceedings of the 2<sup>nd</sup> International Symposium on Phosphorous Chemistry Directed Towards Biology (1987), pages 3-21 (the Caruthers reference) in combination with Nurminen et al, J. Chem. Soc., Perkin Trans. 2 1999, 2551-56 (the Nurminen reference). The instantly claimed processes differ significantly from that of the cited art. The Caruthers reference, as admitted on page 6 of the Office Action, does not disclose use of a  $D^+E^-$  neutralizing agent. The Nurminen reference is alleged to cure this defect. Applicants respectfully disagree because the Nurminen reference shows the use of certain neutralizing agents in the context of reacting diisopropylphosphonite with t-butyl alcohol. The

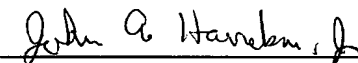
instant invention, in contrast, uses  $D^+E^-$  neutralizing agents in the context of oligomer synthesis. The Nurminen reference, while discussing DNA synthesis generally, nevertheless, does not show equivalent reactions for DNA synthesis. Even if  $D^+E^-$  gives a faster rate of reaction in reaction of the Nurminen reference, it does not necessarily follow that the same effect would be found by using  $D^+E^-$  in the instant process. Thus, even if one were to combine the teachings, one would not arrive at any instantly claimed invention. As such, Applicants respectfully submit that the rejection is improper and should be withdrawn.

Claims 98-101, and 103 stand rejected as allegedly obvious over the Caruthers reference in combination with the Nurminen reference. For reasons entirely analogous to those discussed in the preceding paragraph, the Nurminen reference does not cure the defects found in the Caruthers reference. No instantly claimed invention is arrived at by combining the cited art. As such, Applicants respectfully request reconsideration and withdrawal of the rejection..

Applicants submit that all of the claims presently before the Examiner patentably define the invention over the prior art and are otherwise in condition for ready allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Respectfully submitted,

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